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MICRO-CAPSULES FOR THE SUSTAINED RELEASE OF DRUGS

The present invention relates to a new type of micro-capsule or micro-bead for the sustained administration of drugs and to a procedure for their preparation.

A large variety of administration systems have been proposed for drugs that require administration over a long time period. The strategy described in the literature as the most successful is that of micro-encapsulation of the drug to administer in a polymer material of the biodegradable and biocompatible polyester type, such as polylactic-co-glycolic (PLGA). There are a large number of bibliographic references to this strategy, such as: USP 5,445,832; ES 2009346; CH 661 206; CH 665 558; ES 2037621; USP 4,652,441; ES 2020890; USP 4,728,721; USP 5,330,767; USP 4,917, 893; USP 4,652,441; EP 0 145 240; EP 0 2020 065; EP 0 190 833, among others for example.

These polymers have the peculiarity that they are degraded slowly within the body releasing the drug contained inside, and the products of this degradation (lactic acid and glycolic acid) are naturally present within the organism.

In the micro-capsules described in the literature of the state of the art it is very hard to achieve a satisfactory modulation of the encapsulated drug release, and to avoid an initial large drug release, as this can only be achieved by changing the composition of the polymer (the ratio of lactic-glycolic acid or the molecular weight thereof), which usually implies making important changes in the procedure for the production of the micro-capsules every time a modification in the drug release profile is desired.

In the article published by Pitt el al. in the Journal of Biomedical Materials Research, Vol. 13, pg 497-507, 1979, it is described that tributyl citrate accelerates the release of drugs, for example, progesterone, in microcapsules of polylactic polymers.

As a fruit of our research, we have surprisingly discovered that the addition of small amounts of citric acid esters, to the polymer constituting the micro-capsules, allows a very effective modulation of the liberation characteristics of the micro-capsules obtained, without the need to modify the composition of the polymer.

In the present specification the term modulating release from microcapsules is understood to mean a reduction in the initial release of encapsulated drug and a release of said drug that is almost linear in time. It is both surprising and unexpected, in view

of that described by Pitt et al. that the incorporation of small amounts of citric acid ester into the microcapsule preparation of lactic-co-glycolic polymer that encapsulate a peptide of pharmaceutical interest allows the release of the drug to be almost linear and without the presence of sudden initial releases of the drug.

Therefore, the object of this invention consists of providing pharmaceutical of prepartions micro-capsules of polymers of lactic and glycolic acid plastified with small quantities of citric acid esters and which contain peptides.

The present invention also comprises the preparation and use of the aforementioned microcapsules.

The citric acid esters useful for the purposes of the present invention are those normally used as plasticizers for pharmaceutical polymers, such as triethyl citrate, tributyl citrate and acetyl tributyl citrate. Use of triethyl citrate is preferable.

By peptides of pharmaceutical interest it is understood:

- analogues of LHRH such as tryptoreline, leuprolide, gosereline, busereline or cetrorelix
- analogues of somatostatin such as somatostatin or octreotide
- analogues of human calcitonin such as salmon calcitonin or carbocalcitonin.

The preparation of the micro-capsules can be carried out following any of the methods described in the literature such as, for example, those described in the USP 3,773,919. By way of description and without limitation thereto, the different procedures for producing micro-capsules of the invention would be grouped into the following sections:

a) Method of coacervation:

A solution of polymer is prepared along with tri-ethyl citrate in a suitable solvent. The drug to be encapsulated is suspended in the polymer and plasticiser solution and a non-solvent of the polymer is added to force deposition of the polymer on the drug crystals. Examples of these procedures without using plasticiser can also be found in documents such as ES 2009346 or EP 052 510.

b) Double Emulsion Methods:

The drug to be encapsulated is dissolved in water or in a solution of some other co-adjuvant in is emulsified in a solution of the polymer and the plasticiser in a suitable solvent such as dichloromethane for example. The resulting emulsion is in turn emulsified in water or in an aqueous solution of an emulsifier such as polyvinylic alcohol. Once this second emulsion has been carried out the solvent in which the polymer was dissolved is eliminated through evaporation or extraction. The resulting micro-capsules are obtained directly by filtration. Examples of these procedures that do not use the plasticiser can also be found in documents such as USP 4,652,441.

c) Simple Emulsion Method:

The drug to be encapsulated, the polymer and the plasticiser are dissolved together in a suitable solvent. This solution is emulsified in water or a solution of an emulsifier such as polyvinyl acid and the organic solvent eliminated by evaporation or extraction. The resulting micro-capsules are recovered by filtration. Examples of these procedures that do not sue the plasticiser can also be found in documents such as USP 5,445,832.

d) Methods of solvent evaporation:

The drug to be encapsulated, the polymer and the plasticiser are dissolved together in a suitable solvent. This solution is evaporated to dryness and the resulting residue reduced down to a suitable size. Examples of this procedure, although not using the plasticiser, can be also be found in documents such as GB 2,209,937.

In the present invention, in all cases, the citric acid ester is deposited along with the polymer, plastifying it and advantageously modifying the hydrophobicity, flexibility and coating capacity characteristics of the polymer and the release profile of the micro-capsules obtained.

This is reducing the initial release of the encapsulated drug and making this release almost linear in time.

The present invention is now described by means of following, non-limiting examples:

EXAMPLE 1: Production of micro-capsules, containing leuprolide acetate, which

presents a drug release profile suitable for one month.

3 g of tri-ethyl citrate and 1.45 g of lactic-co-glycolic polymer (mw = 50000 with monomer ratio of 1/1) are dissolved in 50 ml of dichloromethane. When the polymer is fully dissolved 67 mg of leuprolide acetate are added and then suspended by sonication.

63 g of silicone of 350 cts is added slowly with intensive stirring. And when all the silicone has been added the content of the reactor is poured onto 2.5 l of n-heptane and stirred for 1 hour.

The micro-capsules are recovered by filtration and dried under vacuum for 48 hours.

EXAMPLE 2: Production of micro-capsules with one-month release containing octreotide acetate.

2 g of tri-ethyl citrate and 1.45 g of lactic-co-glycolic polymer (mw = 50000 with monomer ratio of 1/1) are dissolved in 50 ml of dichloromethane. When the polymer is fully dissolved 67 mg of octreotide acetate are added and then suspended by sonication.

70 g of silicone of 350 cts is added slowly with intensive stirring. And when all the silicone has been added the content of the reactor is poured onto 2.5 l of n-heptane and stirred for 1 hour.

The micro-capsules are recovered by filtration and dried under vacuum for 48 hours.

EXAMPLE 3: Production of micro-capsules with a three-month release profile containing Triptoreline acetate.

2 g of tri-ethyl citrate and 1.45 g of lactic-co-glycolic polymer (mw = 50000 with monomer ratio of 1/1) are dissolved in 50 ml of dichloromethane. When the polymer is fully dissolved 45 mg of triptoreline acetate are added and then suspended by sonication.

70 g of silicone of 350 cts is added slowly with intensive stirring. And when all the silicone has been added the content of the reactor is poured onto 2.5 l of heptane and stirred for 1 hour.

The micro-capsules are recovered by filtration and dried under vacuum for 48 hours.

EXAMPLE 4: *In vitro* determination of the drug release by the micro-capsules obtained.

MATERIAL NEEDED:

12 plastic 10-ml tubes with lid.

1 rack for tubes.

PROCEDURE:

Approximately 10 mg of micro-capsules containing leuprolide obtained according to example 1 are weighed into 12 10-ml tubes.

To each tube 2 ml of phosphate buffer 1/30 M and pH = 7.0 are added.

Each tube is gently shaken to suspend the micro-capsules in the buffer, the tubes are sealed and placed in an oven at 37° C.

Taking samples for the control of the hydrolysis is carried out in accordance with the following table:

Table 1: Taking samples for analysis of leuprolide released.

Time	Tube no.	Type of analysis
1 h	1, 2	Supernatant
3 h	3	Supernatant
6 h	4	Supernatant
1 d	5 and 6	Pellet
2 d	7	Pellet
4 d	8	Pellet

Point	Tube no.	Type of analysis
8d	10	Pellet
11d	1 and 11	Pellet
14d	2	Pellet
18d	3 and 12	Pellet
23d	9	Pellet
29d	4 and 5	Pellet

The analysis of leuprolide released is carried out by HPLC in the following conditions:

COLUMN: Kromasil C-8; 25x0.45 cm

ELUENT: Acetonitrile/water 30/70 + 0.05% trifluoracetic acid

FLOW RATE:1 ml/min

DETECTION: UV 280 nm.

The samples are taken at the times indicated in table 1 and the analysis carried out by quantifying the peptide released in the supernatant (supernatant analysis) or the residual peptide inside the micro-capsule (pellet analysis) depending on the hydrolysis time, as indicated in table 1.

The result of this analysis is indicated in Figure 1. In this figure, the results obtained are compared with a control assay performed with leuprolide microcapsules in which diethyl citrate has not been incorporated, in accordance with the method of example 1 .